REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. DISPOSITION OF THE CLAIMS

Claims 1-2, 25-29, 31-33, and 38-42 are currently being amended.

Claims 43-45 are being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-2, 22-29, 31-33, and 38-45 are under examination in this application. Claims 30 and 34-37 are withdrawn as non-elected.

This amendment adds no new matter. The amendment to the specification and claims to recite "human, humanized, or chimeric monoclonal antibody" is supported by the underlying international application PCT/FR2003/002713 (see English abstract, line 1) from which the present application is the national stage.

II. OMITTED REFERENCES IN INFORMATION DISCLOSURE STATEMENT

The Office stated, "The foreign references and non-patent literature documents listed on IDS are not considered because applicant fails to submit copies of those references." Office Action, page 2, last 2 lines.

As noted in the Information Disclosure Statement filed March 11, 2005, "Copies of the documents are not being provided since copies should have been provided directly by WIPO under an exchange program between the PTO, the EPO and the JPO."

Nevertheless, to expedite prosecution, Applicants submit herewith the missing references.

III. OBJECTIONS

The Office objected to the specification and claims (Office Action, page 3, paragraphs 4-5).

A. Objections to the Specification

The Office objected to the specification for use of trademarks without capitalization and accompanying generic terminology.

As suggested by the Office, Applicants have appropriately corrected the specification. In the body of the specification, "Remitogen®" has been replaced with "REMITOGEN® (apolizumab)" and "Rutixan®" has been replaced with "RITUXAN® (rituximab)". Table 1 (pages 8-10) has been similarly revised to capitalize trade names and refer to generic terminology, in compliance with M.P.E.P. § 608.01(v). Accordingly, Applicants consider this objection obviated by amendment.

B. Objection to the Claims

The Office objected to the claims for the recitation of "humanized chimeric monoclonal antibody". Applicants have amended the relevant claims to recite "human, humanized, or chimeric monoclonal antibody". Applicants consider this objection obviated by this amendment.

The Office objected to claims 31-33 for dependency on withdrawn claim 30. As impliedly suggested by the Office, claim 31 has been amended to depend from claim 1. Applicants consider this objection obviated by this amendment.

The Office objected to claims 2, 32, 35, and 38 for the recitation of "CD16 receptor expressing effector cells". Applicants respectfully traverse this objection. None of the claims explicitly recite "CD16 receptor expressing effector cells". Claims 1-2, 25-27, 38-39 recite "CD16 *receptor-expressing* effector cells" and claim 32 recites "*CD16-receptor-expressing* effector cells". Both recitations would be understood by a person of ordinary skill in the art in line with the Office's observation that CD16 is a cell surface receptor. Accordingly, Applicants request that this objection be withdrawn.

IV. INDEFINITENESS

Applicants have obviated this ground of rejection by amendment.

The claims stand rejected as indefinite due to the recitation of "wherein said antibody". Applicants have amended the claims to recite "wherein said human, humanized, or chimeric monoclonal antibody" to specify more clearly which antibody "said antibody" refers to.

Claims 27-28 and 33 stand rejected as indefinite for limitations beginning with "in particular". Applicants have deleted from claims 27-28 and 33 the "in particular" limitations. The deleted limitations now appear in new claims 43-45.

V. WRITTEN DESCRIPTION/NEW MATTER

Claim 32 stands rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. The Office asserts that "the expression line for apolizumab" is not supported in the specification.

Applicants traverse. The specification as filed discloses apolizumab by its brand name Remitogen® (see page 1, line 29). Claim 13 as originally filed, now canceled, referred to "the expression line for Remitogen®". Claim 32 corresponds to claim 13 with "the expression line for Remitogen®" replaced by "the expression line for apolizumab".

In support, Applicants attach a definition of "apolizumab" from the National Cancer Institute "NCI Drug Dictionary" identifying "Remitogen" as the U.S. brand name of "apolizumab" (see http://www.nci.nih.gov/Templates/drugdictionary.aspx?CdrID=38451).

Accordingly, "the expression line for apolizumab" is fully supported by the specification as filed. Applicants ask the Office to withdraw this ground of rejection.

VI. ANTICIPATION

The claims stand rejected as anticipated under 35 U.S.C. § 102(b) over WO 01/77181 as evidenced by counterpart US 2003/0175969. Applicants respectfully traverse.

The Office states (Office Action, page 5, 7-17):

> Beliard et al. teach human anti-Rhesus D monoclonal antibody made in rat myeloma host cell YB210 that has particular glycosylation profile in the Fc region wherein said human anti-Rhesus D monoclonal antibody exhibits enhanced CD16 mediated ADCC function compared to commercially available homologous antibodies (e.g. see Examples 1-3 on pages 6-17).
>
> Given that the prior art human anti-Rhesus D monoclonal antibody is made in the same YB210 host cells as the claimed antibody, the prior art antibody would inherently have the properties, e.g. an ADCC rate of greater than 100% at a concentration of 10 ng/ml or less, induction of cytokines such as interleukine or TNFs by Jurkat CD16 cells or CD16 expressing effector cells of the immune system. Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not have the properties as recited in the claims.

The rejection is deficient because the Office makes improper use of inherency to assert that WO 01/77181 satisfies the limitation "ability to induce a rate of production of at least one cytokine by the Jurkat CD16 cell or a CD16 receptor-expressing effector cell of the immune system of greater than 60%, compared with the same antibody produced in a CHO line or with a commercially available homologous antibody".

The present specification refers directly to WO 01/77181 and distinguishes the reference, stating (page 2, line 36, to page 3, line 13):

> We have shown, in our application WO 01/77181 (LFB), the importance of selecting cell lines for producing antibodies exhibiting strong ADCC activity of the FcγRIII (CD16) type. We have found that modifying the glycosylation of the constant fragment of the antibodies resulted in an improvement in the ADCC activity in rat myeloma lines such as YB2/0, the glycan structures being of the biantennary type, with short chains, a low degree of sialylation, nonintercalated terminal attachment point mannoses and GlcNAcs and a low degree of fucosylation.
>
> Now, in the context of the present invention, we have discovered that the advantage of exhibiting a high affinity for CD16 can be further enhanced by additional tests aimed at choosing the antibodies that induce cytokine production.

Thus, the present invention is distinguished from WO 01/77181 by the selection of antibodies which satisfy the limitation "ability to induce a rate of production of at least one cytokine by the Jurkat CD16 cell or a CD16 receptor-expressing effector cell of the immune system of greater than 60%, compared with the same antibody produced in a CHO line or with a commercially available homologous antibody".

The present specification explains the necessary selection for arriving at the claimed invention (page 7, line 36, to page 8, line 3):

> [Y]he antibody may, firstly, be selected for its CD16 receptor affinity, and then assayed and selected as described above for its properties of inducing the production of a cytokine, in particular IL 2, by Jurkat CD16 cells, or IFNγ by CD16-expressing effector cells from the blood.

The present specification describes the advantages of the claimed invention as follows (page 8, lines 5-8):

> Such antibodies having this double property of inducing ADCC via CD16 and of inducing the production of IL 2, result in a very substantial stimulation of the cytotoxic activity of effector cells.

The Office relies on the doctrine of inherency in asserting that "the prior art antibody would inherently have the properties . . . ".

It is bedrock patent law that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." M.P.E.P. § 2163.07(a) (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002) (quoting *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002) and *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)).

Here, because WO 01/77181 does not disclose the antibody selection necessary for arriving at the present invention, the Office at best suggests a possibility that a person of ordinary skill in the art following the disclosures of WO 01/77181 would arrive at present

invention. Based on the presumptively correct statements in the specification quoted above discussing WO 01/77181, there is at best a very low probability that the disclosures of WO 01/77181 absent further selection would yield an antibody satisfying the limitation "ability to induce a rate of production of at least one cytokine by the Jurkat CD16 cell or a CD16 receptor-expressing effector cell of the immune system of greater than 60%, compared with the same antibody produced in a CHO line or with a commercially available homologous antibody".

The Office cannot rely on such a probability or possibility, because such reliance is squarely contrary to the controlling case law cited above regarding inherency. Accordingly, WO 01/77181 does not meet the standard for establishing inherency.

VII. OBVIOUSNESS

Claims 1 and 31-33 stand rejected under 35 U.S.C. § 103(a) over US 6,894,149 ("Tso") and EP 1229125 ("Ogawa").

The obviousness rejection is deficient (a) in mischaracterizing the difference between Tso and the claimed invention and (b) in failing to account for the limitation "ability to induce a rate of production of at least one cytokine by the Jurkat CD16 cell or a CD16 receptor-expressing effector cell of the immune system of greater than 60%, compared with the same antibody produced in a CHO line or with a commercially available homologous antibody" in claims 1 and 31-33.

Applicants reserve the right to challenge the prior art status of Tso and Ogawa in the future. For now, Applicants traverse the obviousness rejection for the following reasons.

A. The Office Mischaracterized Tso

The Office erred in stating: "[Tso's] teachings differ from the claimed invention by not describing humanized anti-HLA-DR antibody made in rat myeloma YB210 cells."

In contrast to this statement, Tso differ from the claimed invention, inter alia, by failing to satisfy the limitation "ability to induce a rate of production of at least one cytokine by the Jurkat CD16 cell or a CD16 receptor-expressing effector cell of the immune system of

greater than 60%, compared with the same antibody produced in a CHO line or with a commercially available homologous antibody".

On this basis the rejection is deficient and should be withdrawn.

B. Ogawa Fails To Satisfy The Limitation That Is Missing In Tso

The Office nowhere asserts that the combination of Tso and Ogawa directly satisfies the limitation "ability to induce a rate of production of at least one cytokine by the Jurkat CD16 cell or a CD16 receptor-expressing effector cell of the immune system of greater than 60%, compared with the same antibody produced in a CHO line or with a commercially available homologous antibody". Instead, the Office relies on inherency (Office Action, page 6, lines 17-22):

> Additionally, such humanized anti-HLA-DR antibodies made in rat myeloma cell YB210 would inherently have the properties of an ADCC rate of greater than 100% at a concentration of 10 ng/ml or less and a rate of IL-2 production by a CD16 expressing effector cell of the immune system of greater than up to 1000% at a concentration of 10 ng/ml or less compared with the same antibody expressed in CHO cell line.

While the Office appears to refer to the limitations of claim 2 in the passage quoted above, Applicants address the relevance of such argument to the rejected claims 1 and 31-33.

As explained above in traversing the anticipation rejection, it is legal error to rely on obviousness where, as here, there is at best a possibility that the claim limitations would be met. Moreover, reliance on inherency has been criticized as inappropriate in asserting obviousness. *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

Accordingly, the obviousness rejection is deficient and should be withdrawn.

VIII. PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING (ODP)

The claims stand provisionally rejected for obviousness-type double patenting over specific claims of copending applications 10/551,819 and 10/575,218 and 11/039,877.

Applicants request that this ground of rejection be held in abeyance pending indication of allowable subject matter.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

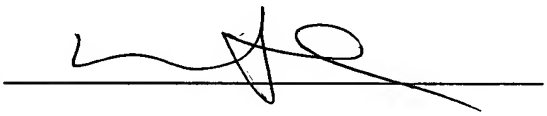
The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 16-JAN-2009

By 

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